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## Effect of a Somatostatin Analogue on the Vasopressin Pathway in Patients With ADPKD



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**A**utosomal dominant polycystic kidney disease (ADPKD) is characterized by high activity of adenylyl cyclase (AC) in renal tubular cells, which stimulates the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). This results in high intracellular cAMP levels, which lead to aberrant renal tubular epithelial cell proliferation and chloride-driven fluid excretion in the kidney, causing cyst formation and growth. Ultimately these processes lead to kidney failure, with a need for renal replacement therapy such as dialysis or renal transplantation.

The vasopressin V2 receptor antagonist tolvaptan has the ability to inhibit the activity of AC and to lower cAMP levels. Tolvaptan can therefore attenuate kidney growth and the rate of renal function decline.

However, the effect of tolvaptan is limited to the kidney, and its aquaretic side effects hamper widespread clinical use. Therefore there is still an unmet need for new therapies to slow disease progression in ADPKD. In this respect, somatostatin analogues are of interest, as somatostatin analogues also have the ability to lower intracellular cAMP levels by inhibiting the activity of AC in kidney as well as liver tissue. These drugs decrease the growth rates of liver and kidney volume in ADPKD.<sup>1–5</sup>

Because both drugs lower cAMP levels by inhibiting the activity of AC, it may be that there is a pharmacodynamic interaction between somatostatin analogues and tolvaptan. Interestingly, older experimental studies have suggested involvement of somatostatin in renal water handling, causing either a

**Table 1.** Baseline characteristics

Characteristic	Standard care (n = 152)	Somatostatin analogue (n = 153)
Female, n (%)	81 (53.3)	82 (53.6)
Age, yr	48.5 ± 7.22	48.2 ± 7.41
BMI, kg/m <sup>2</sup>	27.1 ± 4.9	26.9 ± 4.5
SBP, mm Hg	133 ± 14	132 ± 13
DBP, mm Hg	82 ± 10	82 ± 9
AHT, n (%)	137 (90.1)	140 (91.5)
RAASi, n (%)	126 (82.9)	125 (81.7)
Diuretics, n (%)	60 (39.5)	57 (37.3)
eGFR, ml/min per 1.73 m <sup>2</sup>	50 ± 11	51 ± 12
htTKV, ml/m	1028 (720–1678)	1138 (779–1723)
PKD mutation, n (%)		
PKD1 truncating	64 (42.1)	76 (49.7)
PKD1 nontruncating	41 (27.0)	33 (21.6)
PKD2	30 (19.7)	30 (19.6)
No mutation detected	7 (4.6)	8 (5.2)
Missing	10 (6.6)	6 (3.9)
Urine volume, L/24 h	2.44 ± 0.84	2.28 ± 0.69
FWC, L/24 h	−0.68 ± 1.00	−0.72 ± 0.77
FFWC, %	−1.28 ± 2.26	−1.52 ± 1.60
Plasma osmolality, mOsm/kg	288 ± 5.79	289 ± 5.57
Urine osmolality, mOsm/kg	389 ± 116	401 ± 117
Sodium excretion, mmol/24 h	170 ± 73.7	156 ± 56.6
Osmol excretion, mOsm/24 h	903 ± 299	867 ± 225
Plasma copeptin, pmol/l	9.6 (5.8–14.7)	9.9 (5.5–18.5)

AHT, anti-hypertensive therapy; BSA, body surface area; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume; PKD, polycystic kidney disease; RAASi, RAAS inhibitors; SBP, systolic blood pressure. Variables are presented as mean ± SD, or as median (interquartile range) in the case of nonnormal distribution. P values are calculated using independent-sample *t*-test in case of normal distribution, Mann–Whitney *U* in case of nonnormal distribution, and  $\chi^2$  in case of categorical data.

diuretic or an antidiuretic effect, dependent on vasopressin levels.<sup>6–9</sup> A more recent study observed a lower urine volume in *PKD1* mice receiving a combination of a somatostatin analogue and tolvaptan in comparison to mice receiving tolvaptan alone.<sup>10</sup> This suggests that there indeed may be an interaction between the somatostatin and vasopressin pathways.

In this study, we therefore investigated whether the somatostatin analogue lanreotide has an effect on vasopressin levels and renal water handling in patients with ADPKD. The Materials and Methods section can be found in the [Supplementary Material](#).

## RESULTS

### Subject Characteristics

A total of 305 patients were included, 53.4% of whom were female. The estimated glomerular filtration rate (eGFR) was 50 ± 11 ml/min per 1.73 m<sup>2</sup> and the height-adjusted total kidney volume (htTKV) 1089 (754–1670) ml/m. There were no differences in baseline characteristics between patients randomized to standard care (n = 152) or lanreotide (n = 153) ([Table 1](#)).

### Parameters of Aquaresis in Patients Receiving Lanreotide or Standard Care

At baseline, there were no statistically significant differences in 24-hour urine volume, free water clearance (FWC), fractional free water clearance (FFWC), plasma osmolality, urine osmolality, sodium excretion, osmol excretion, and copeptin between patients randomized to standard care or lanreotide ([Table 1](#)).

From baseline to week 12, there were no statistically significant differences in change in parameters of aquaresis, between patients receiving standard care or lanreotide ([Table 2](#)). Total osmol excretion in the 2 groups was similar at baseline (903 ± 299 vs. 867 ± 225 mOsm/24-hour, *P* = 0.3) and after 12 weeks (882 ± 262 vs. 845 ± 253 mOsm/24-hour, *P* = 0.2), and also change in osmolar excretion at 12 weeks was not different between both groups (−23 ± 242 vs. −36 ± 202 mOsm/24-hour, *P* = 0.6).

### Subgroups With Possible Differences in Aquaresis

The association of copeptin with change in 24-hour urine volume or FFWC was not statistically significant different between patients receiving standard care or lanreotide (interaction term: baseline copeptin\*–treatment group, *P* = 0.77 and *P* = 0.67, respectively). The association of use of diuretics with change in 24-hour volume or FFWC was also not statistically significant different between the 2 study groups (interaction term: use of diuretics\*treatment group, *P* = 0.84 and *P* = 0.97 respectively). The association

**Table 2.** Change in parameters of aquaresis from baseline to week 12 in patients receiving lanreotide versus standard care

Variable	Standard care	Somatostatin analogue	Mean difference (95% CI)	<i>P</i>
Change urine volume (L/24 h)	0.071 ± 0.70	−0.020 ± 0.63	−0.09 (−0.25 to 0.06)	0.25
Change FWC (L/24 h)	0.16 ± 0.77	0.09 ± 0.64	−0.08 (−0.25 to 0.09)	0.39
Change FFWC (%)	0.25 ± 1.73	0.20 ± 1.32	−0.05 (−0.42 to 0.32)	0.79
Change plasma osmolality (mOsm/kg)	−0.32 ± 4.91	0.77 ± 5.09	1.09 (−0.08 to 2.26)	0.07
Change urine osmolality (mOsm/kg)	−22.1 ± 98.5	−9.99 ± 98.5	12.1 (−10.8 to 35.1)	0.30
Change sodium excretion (mmol/24 h)	−12.0 ± 73.0	−7.64 ± 59.1	4.3 (−11.2 to 19.8)	0.58
Change osmol excretion (mOsm/24 h)	−23 ± 242	−36 ± 202	26.7 (−64.9 to 40.2)	0.64
Change plasma copeptin (pmol/l)	−0.07 ± 5.58	−0.93 ± 13.5	−0.86 (−3.23 to 1.52)	0.48

eGFR, estimated glomerular filtration rate; FFWC, fractional free water clearance; FWC, free water clearance. Data are expressed as mean ± SD. Differences between groups were tested with an independent-sample *t*-test.

**Table 3.** Change in parameters of aquaresis from baseline to week 12 in patients receiving lanreotide versus standard care stratified according to eGFR

Variable	eGFR ≤ 50 ml/min per 1.73 m <sup>2</sup>				eGFR > 50 ml/min per 1.73 m <sup>2</sup>			
	Standard care	Somatostatin analogue	Mean difference (95% CI)	P	Standard care	Somatostatin analogue	Mean difference (95% CI)	P
Number (n)	67	80		–	85	73		–
Change urine volume (L/24 h)	–0.04 ± 0.68	0.00 ± 0.54	0.04 (–0.17 to 0.24)	0.72	0.15 ± 0.71	–0.05 ± 0.73	–0.20 (–0.43 to 0.04)	0.10
Change FWC (L/24 h)	0.01 ± 0.78	0.19 ± 0.52	0.18 (–0.04 to 0.41)	0.11	0.28 ± 0.75	–0.04 ± 0.74	–0.32 (–0.57 to –0.07)	<b>0.01</b>
Change FFWC (%)	–0.06 ± 2.11	0.49 ± 1.32	0.55 (–0.08 to 1.18)	0.09	0.48 ± 1.34	–0.16 ± 0.24	–0.64 (–1.09 to –0.20)	<b>0.005</b>
Change plasma osmolality (mOsm/kg)	–0.21 ± 5.39	0.89 ± 5.31	1.10 (–0.71 to 2.91)	0.23	–0.41 ± 4.54	0.62 ± 4.88	0.78 (–0.50 to 2.57)	0.18
Change urine osmolality (mOsm/kg)	–6.5 ± 90.9	–17.0 ± 66.8	–10.5 (–37.0 to 16.0)	0.43	–34.4 ± 103.0	–1.9 ± 125.5	32.5 (–4.82 to 69.9)	0.09
Change sodium excretion (mmol/24 h)	–14.3 ± 72.8	–13.4 ± 57.7	11.0 (–20.9 to 22.6)	0.94	–10.1 ± 73.6	–0.7 ± 60.5	9.46 (–13.1 to 32.0)	0.41
Change osmol excretion (mOsm/24 h)	0.02 ± 268	–54.9 ± 188	–55.0 (–135.0 to 25.0)	0.18	–42.1 ± 219	–12.8 ± 217	29.3 (–43.7 to 102.3)	0.43
Change plasma copeptin (pmol/l)	0.24 ± 7.20	0.86 ± 11.02	0.62 (–2.54 to 3.78)	0.70	–0.32 ± 3.8	–2.86 ± 15.5	–2.53 (–6.05 to 0.99)	0.12

CI, confidence interval; eGFR, estimated glomerular filtration rate; FFWC, fractional free water clearance; FWC, free water clearance.

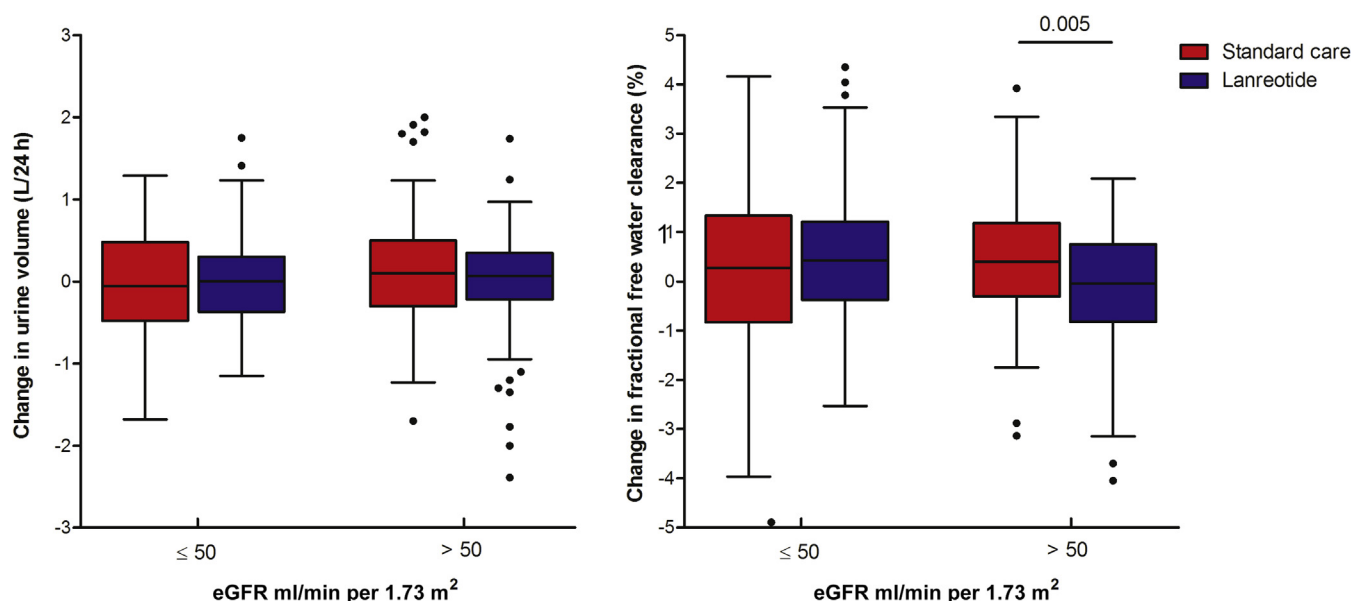
Data are expressed as mean ± SD. Differences between groups were tested with an independent-sample *t*-test. Bold *P* values indicate statistical significance.

between baseline eGFR and change in FFWC was significantly different between patients receiving standard care or lanreotide (interaction term: baseline eGFR\*treatment group, *P* = 0.001). In patients receiving lanreotide, there was a significant negative association between eGFR and change in FFWC (Standardized [St.]  $\beta$  = –0.24, *B* = –0.03, 95% confidence interval [CI] = –0.05 to –0.009, *P* = 0.005), whereas in patients receiving standard care there was a significant positive association (St.  $\beta$  = 0.18, *B* = 0.03, 95% CI = 0.002–0.06, *P* = 0.01) (Supplementary Figure S1). The difference in association between baseline eGFR and change in 24-hour urine volume did not reach statistical significance (interaction term: baseline eGFR\*treatment group, *P* = 0.08).

When patients were divided according to the mean eGFR of the study population (eGFR ≤ or >50 ml/min per 1.73 m<sup>2</sup>), we observed no differences in change in

parameters of aquaresis in patients with an eGFR ≤50 ml/min per 1.73 m<sup>2</sup>. However, patients with an eGFR >50 ml/min per 1.73 m<sup>2</sup> had a relative decrease in FWC with lanreotide compared to patients receiving standard care (lanreotide –0.04 ± 0.74 L/24 hours, control 0.28 ± 0.75 L/24 hours, difference *P* = 0.01) as well as in FFWC (lanreotide –0.16 ± 0.24%, control 0.48 ± 1.34%, difference *P* = 0.005). The 24-hour urine volume and copeptin levels also decreased in patients receiving lanreotide compared to standard care, although this did not reach formal statistical significance (lanreotide –0.05 ± 0.73 L/24-hour, control 0.15 ± 0.71 L/24-hour, difference *P* = 0.10 and lanreotide –2.86 ± 15.5, control –0.32 ± 3.8 pmol/L, difference *P* = 0.12) (Table 3 and Figure 1).

In line with the results of the above interaction tests, there were no differences in parameters of aquaresis when patients were studied stratified according to

**Figure 1.** Change in 24-hour urine volume (left panel) and fractional free water clearance (right panel) from baseline to T12 in patients receiving standard care or lanreotide, stratified according to mean level of estimated glomerular filtration rate (eGFR) at baseline.

median copeptin level or whether or not they used diuretics ([Supplementary Table S1](#)).

## DISCUSSION

In this *post hoc* analysis of the DIPAK-1 trial, we investigated the possible interaction between the somatostatin and vasopressin pathways on aquaresis. Overall, there were no differences in change in 24-hour urine volume, FWC, FFWC, or copeptin levels in patients with ADPKD receiving 12 weeks of standard care or the somatostatin analogue lanreotide. However, an interaction with baseline eGFR was found, indicating that patients with more preserved kidney function who received lanreotide had a decrease in FWC and FFWC.

Both the somatostatin and the vasopressin V2 receptors co-localize with AC in the basolateral membrane in renal tubular cells of the collecting duct. Nine distinct membrane-bound AC isoforms (AC1–9) have been identified, and each can exert unique effects in various cell types of the kidney.<sup>51</sup> It is currently unknown whether there are specific AC isoforms associated with the vasopressin V2 or somatostatin receptor. If both receptors interact with the same AC isoform, an effect of the somatostatin analogue on renal water handling may be expected. The first studies that proposed the involvement of somatostatin in renal water handling were performed in dogs that had a high vasopressin level. These studies showed a diuretic effect after infusion of somatostatin.<sup>6,S2</sup> In contrast, a study by Walker *et al.* found that intravenous infusion of somatostatin in water-loaded human subjects caused an antidiuretic effect.<sup>7</sup> In addition, these investigators showed that vasopressin levels remained stable in these subjects, concluding that somatostatin has a direct effect on the renal tubule with respect to renal water handling. Based on these data and the aforementioned experimental data, Walker *et al.* hypothesized that the effects of somatostatin may be dependent on levels of vasopressin; that is, with high levels of vasopressin, somatostatin elicits a diuretic effect, and with low levels of vasopressin an antidiuretic effect. This hypothesis was tested by another study group in 1993. They found in rats that the effect was not dependent on vasopressin but rather on somatostatin levels. A low dose of somatostatin had a diuretic and a high dose of somatostatin an antidiuretic effect in the presence or absence of vasopressin.<sup>53</sup> Studies with subcutaneous administration of somatostatin analogues, which is essentially a high dose of somatostatin, did indeed show an antidiuretic effect of this drug in experimental studies.<sup>10,S4,S5</sup>

In our study, we did not observe an effect of the somatostatin analogue lanreotide on aquaresis in patients with ADPKD overall. An explanation for not finding an

effect of lanreotide on the vasopressin pathway could be that this effect was dependent on the characteristics of the included patients. As reasoned above, the effect of somatostatin on aquaresis could be dependent on vasopressin, with lanreotide not having an effect in individuals with higher vasopressin, as is often the case in ADPKD.<sup>56</sup> Furthermore, in previous studies, only healthy subjects were studied who did not use medication that may affect aquaresis. The effect of somatostatin analogues on aquaresis may become less apparent with more severe ADPKD, when tubular function is compromised and urine concentrating defects exist,<sup>57,S8</sup> or when diuretics are used. We therefore tested whether there was an interaction between the effect on aquaresis of treatment and baseline copeptin, eGFR, or use of diuretics. We found no such interaction for baseline copeptin or use of diuretics. We did, however, observe an interaction for the association of baseline eGFR with treatment-induced change in FFWC and a nearly significant interaction with change in 24-hour urine volume. When patients were stratified according to mean eGFR, there was a decrease in FWC and FFWC with lanreotide in patients with an eGFR >50 ml/min per 1.73 m<sup>2</sup>, whereas aquaresis remained stable with lanreotide in subjects with impaired kidney function. No statistically significant differences in 24-hour urine volume were observed. These findings suggest that in ADPKD patients with a more preserved kidney function, lanreotide has an effect on renal water handling, albeit small.

The first studies that investigated the therapeutic effect of somatostatin analogues in ADPKD were underpowered and too short in duration to allow firm conclusions on the renoprotective effect of these drugs.<sup>1–4</sup> A recent larger clinical trial, with balanced baseline characteristics, showed no effect on rate of eGFR loss,<sup>59</sup> but did show a beneficial effect on growth rate of kidney as well as liver volume. Therefore, there may be a place for somatostatin analogues in the treatment of ADPKD patients with symptoms related to an increased intra-abdominal volume. Combination therapy of tolvaptan with a somatostatin analogue may therefore be indicated in such patients. An interaction between the somatostatin and vasopressin pathways could have consequences for the renoprotective effect of tolvaptan as well as its aquaretic side effects when tolvaptan and a somatostatin analogue are used simultaneously. In our study, the decrease in FFWC and FWC that we observed in subjects with preserved renal function seems to be a direct effect of lanreotide and not mediated by vasopressin, as copeptin levels (as surrogate of vasopressin) did not change. If anything, copeptin levels decreased in this patient group, whereas an increase might have been expected if the effect of lanreotide was mediated by vasopressin. Therefore, there may be a possibility that



vasopressin V2 receptor antagonist and somatostatin analogues have synergistic effects in the treatment of ADPKD. Although the anti-aquaretic effect of lanreotide in our study was small and did not lead to a significant effect on 24-hour urine volume, it may have more impact in a situation in which there is excessive free water clearance, as with tolvaptan use. Combination therapy with a somatostatin analogue and tolvaptan may therefore not only result in an additive effect on total kidney volume growth in ADPKD, but may also reduce the aquaretic side effects of tolvaptan. Future studies should investigate this hypothesis.

Our study had limitations. First, our study was open label, and therefore patients in the lanreotide and control group may have adhered differently to dietary recommendations concerning water and osmole intake. However, we did not observe differences in change in parameters of aquaresis and osmolar excretion in the overall group of patients, indicating that it would not have affected our results to a large extent. Second, we included patients with later-stage ADPKD, assessed as an eGFR between 30 and 60 ml/min per 1.73 m<sup>2</sup>, and found an interaction between the effects of lanreotide on aquaresis and baseline kidney function. We cannot exclude, therefore, that stronger effects would be seen in subjects with an eGFR above the inclusion criteria of the present study.

In conclusion, we found that the somatostatin analogue lanreotide may lower free water clearance, but only in ADPKD patients with a relatively preserved kidney function. We hypothesize that when somatostatin analogues are added to tolvaptan for volume reduction in ADPKD, a decrease in polyuria may be expected in patients with preserved kidney function. Whether such an effect is clinically relevant remains to be studied.

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

### Supplementary Materials and Methods.

**Table S1.** Change in parameters of aquaresis from baseline to week 12 in patients receiving lanreotide versus standard care stratified according to copeptin level (upper panel) or use of diuretics (lower panel).

**Figure S1.** Association between baseline eGFR and change in FFWC from baseline to week 12 in patients receiving standard care or lanreotide.

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